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Review Article

Antimicrobial Resistance in Patients with Acute Exacerbation of COPD

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Abstract

Objective: To assess the prevalence of bacterial infection of patients admitted to the emergency room for an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and studied the antimicrobial resistance.

Methods: It was a descriptive and analytical study including patients hospitalized for AECOPD. Bacteriological examination included a cytobacteriological sputum exam and serological tests.

Results: Of the 240 patients enrolled, 175 sputum cultures (73%) were considered significant. Twenty-nine cultures were positive (16.5%) and 31 microorganisms were isolated which the most frequent were *P. aeruginosa* (25.8%), *K. pneumoniae* (16.2%), *H. influenzae* (13%) and *S. pneumoniae* (9.7%). The prevalence of *C. pneumoniae, M. pneumoniae* and *C. burnetii* was respectively 8.4%, 9% and 6.6%. No *L. pneumophila* infection was found. The positive culture are associated with Anthonisen criteria (p = 0.004). Almost half (40.9%) of the isolates were resistant to conventional first line antibiotics [43.7% Amoxicillin-Clavulanic acid].

Conclusion: The low positivity of quantitative sputum bacteriology and the large percentage of resistant strains with a predominance of exclusively multiresistant Pseudomonas can help in the management of patients with AECOPD.

Keywords: AECOPD; Bacterial Infection; Atypical Microorganism; Bacterial Resistance

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory process characterized by a progressive airflow limitation and the destruction of parenchyma. Patients affected by this disease experience frequent exacerbations that favor airway inflammation and often lead to hospitalization. Acute Exacerbation of COPD (AECOPD) is an exaggeration of the symptoms of chronic bronchitis. Currently, the 3 criteria of Anthonisen [1] seem most satisfactory to define the AECOPD: the increase in the volume of expectoration, a change in its appearance that becomes purulent and increased dyspnea. The infectious causes of the exacerbation have probably been underestimated [2]. Since the revision of the recommendations of the French Agency for the Safety of Health Products (AFSSAPS), there are very few publications to report concerning chronic bronchitis and their infectious causes. Bacterial and viral infections of the lower respiratory tract account for approximately 80% of all exacerbations [3,4]. On the other hand, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* are common human pathogens causing asymptomatic or severe, high and low respiratory tract infections with seroprevalence in the general population of up to 70% and 60%, respectively [5,6]. These infections are usually not identified in general health care because the etiology of respiratory tract infections is investigated in only a small proportion of patients, i.e. those who do not respond to conventional antimicrobial therapy or present with severe pneumonia [7]. The role of these pathogens in AECOPD is controversial [8,9]. Very few publications exist on other atypical organisms such as *Coxiella burnetii* and *Legionella pneumophila* [9].

Our study of 100 consecutive Tunisian patients presenting with COPD exacerbation shows an overall prevalence of *C. pneumoniae* acute infection of 11%. This figure is supported by other international study results; it therefore seems reasonable to recommend the diagnosis of this infection in this particular context, with the aim of implementing an adequate antimicrobial treatment [10]. So, a precise definition of bacteria in AECOPD is important to understand and guide the antimicrobial therapeutic approach [11]. Es-

pecially since there are non-fermenting gram-negative bacilli such as *P. aeruginosa* and *Acinetobacter baumannii* that are reported for their multidrug resistance (multiresistance bacteria or BMR) [12].

Patients and Methods

Study design

We conducted a prospective observational study in the Emergency department of three university hospitals (Monastir, Mahdia, and Sousse) located in the South-East of Tunisia, from May 2013 to March 2015.

The study population consisted of patients aged over 40 years diagnosed with COPD stages 1 - 4 as defined by the Global initiative for chronic obstructive lung disease (GOLD), with an acute exacerbation (onset ≤ 14 days) [13]. Acute respiratory failure was defined as a worsening of dyspnea associated with at least two of the following characteristics: respiratory rate ≥ 24 breaths/min, arterial partial pressure of carbon dioxide ≥ 45 mmHg, arterial pH ≤ 7.35. A chest radiograph confirming the absence of pneumonia was required. Exclusion criteria were outpatient status; evidence of bronchiectasis, pneumonia, malignancy or severe immunosuppression, antimicrobial treatment received in the 10 days proceeding COPD exacerbation or need for mechanical ventilation. History, physical examination, arterial blood gas, and x-ray results were recorded for all included patients. Except for antibiotics, patients received instrumental and medical therapy according to current guidelines [13]. This study was part of a larger double-blind randomized study aiming at comparing two lines of antibiotic therapy: a two-day treatment with levofloxacin versus a 7-day treatment using the same molecule. Our study is a follow-up of a similar study previously performed in the same setting [14].

Ethics

The Ethics committee in research of Sousse hospital approved the study; it was registered in the ClinicalTrials.gov database under the number NCT02067780. Written informed consent was obtained from all patients.

Microbiological management

Baseline sputum specimens were systematically collected. Semi-quantitative bacterial cultures were performed at the Microbiology laboratory of the university hospital of Monastir as recommended [15]. Results were considered significant if a bacterium of interest was isolated with a count of at least 107 CFU/mL.

Four ml of the blood sample should be taken for serological tests at admission (day 0) and after 15 days for research of a typical microorganisms: *Mycoplasma pneumoniae, Coxiella burnetii, Chlamydophila pneumoniae* and *Legionella pneumophila.*

Results

The positivity of the culture was not related to the age of the patients, nor to the number of the exacerbations per year, nor to the smoking. No other clinical parameter was significant for the prediction of a bacterial infection. On the other hand, Anthonisen's criteria can be considered as indirect proof of a positive culture [44.4% of patients with a positive culture presenting 3 criteria of Anthonisen versus 22.5% of patients presenting these 3 criteria but having a negative culture] (p = 0.04) (Table 1)

SD: Standard Deviation; NS: Not Significant; p significant ≤ 0.05.

Twenty-nine cultures were positive (16.5%) and 31 germs were isolated. The 4 most frequently isolated species were *P. aeruginosa* (25.8%), *K. pneumoniae* (16.2%), *H. influenzae* (13.0%) and *S. pneumoniae* (9.7%). Four samples are presenting associations [17]. The prevalence of C. pneumoniae, M. pneumoniae and C. burnetii was respectively 8.4%, 9% and 6.6%. No L. pneumophila infection was found. In total, there were 10 associations (Table 2).

Characteristics	All patients N = 240	Culture		
		Negative N = 211	positive N=29	p
- Age (years, moy ± SD)	68.3 ± 10.5	68.14 ± 10.7	69.52 ± 8.87	NS
- Sex				
Male	218 (90.8)	190 (90)	28 (96.6)	NS
Female	22 (9.2)	21 (10)	1(3.4)	
-Tabac (P/ Year)	70.2 ± 105	78.41 ± 144.42	85.62 ± 143.03	NS
-Nombre annuel d'EABPCO (moyenne ± ET)	2.7 ± 1.9	2.74 ± 1.92	2.92 ± 1.77	NS
-Clinical History of Exacerbation: Anthonissen criteria				
One criteria	65 (39.4)	59 (42.8)	6 (22.2)	0.04
Two criteria	57 (34.5)	48 (34.8)	9 (33.3)	
Three criteria	43 (26.1)	31 (22.5)	12 (44.4)	
Follow-up				
Readmission at 6 months	56 (39.3)	44 (37.3)	12 (54.5)	0.02
Readmission at 12 months	17 (54.8)	13 (48.1)	4 (100)	0.05

Table 1: Characteristics of patients admitted to the emergency room for AECOPD.

Pathogen	Number
Conventional bacteriological cultures (N=175)	
Pseudomonas aeruginosa	8 (25.8%)
Klebsiella pneumoniae	5 (16.2%)
Haemophilus influenzae	4 (13%)
Escherichia coli	3 (9.7%)
Streptococcus pneumoniae	3 (9.7%)
Acinetobacter baumannii	2 (6.4%)
Proteus mirabilis	1 (3.2%)
Providencia spp	1 (3.2%)
Branhamella catarrhalis	1 (3.2%)
Acinetobacter spp	1 (3.2%)
Haemophilus parainfluenzae	1 (3.2%)
Staphylococcus aureus	1 (3.2%)
Serological tests	
Mycoplasma pneumoniae (n=166)	15 (9%)
Chlamydophila pneumoniae (n=166)	14 (8.4%)
Coxiella burnetii (n=91)	6 (6.6%)
Legionella pneumophila (n=124)	0 (0%)
Associations (N=10)	
Acinetobacter spp / Providencia	1 (10%)
Klebsiella pneumoniae / Pseudomonas aeruginosa	1 (10%)
Klebsiella pneumoniae / Haemophilus influenzae	1 (10%)
Klebsiella pneumoniae / Proteus mirabilis	1 (10%)
Escherichia coli / Chlamydia pneumoniae	1 (10%)
Haemophilus influenzae / Chlamydia pneumoniae	1 (10%)
Pseudomonas aeruginosa / Coxiella burnetii	1 (10%)
Pseudomonas aeruginosa / Mycoplasma pneumoniae	2 (20%)
Streptococcus pneumoniae / Chlamydia pneumonia	1 (10%)

Table 2: List of pathogens recovered from the sputum and blood samples of the 240 patients included into the study.

The present study [16] on the bacterial flora of AECOPD, showed a low positivity of quantitative bacteriology of sputum and a large percentage of resistant strains 40.9% with a predominance of pseudomonas which are exclusively multiresistant and a predominance of resistance to aminopenicillins [43.7% for Amoxicillin-clavulanic acid] (Table 3).

Discussion

Early initiation of antibiotic therapy is the cornerstone for treating a bacterial infection which is associated with an improvement in the clinical outcome of patients [17,18]. In return, exposure to antibiotics leads, on the one hand, a selection pressure with a risk of emergence of bacterial resistance and, on the other hand, potential adverse effects, and this with a sometimes-substantial cost [19]. In fact, non-fermenting gram-negative bacilli such as *P. aeruginosa* and *Acinetobacter baumannii* are reported for their multidrug resistance (multiresistance bacteria or BMR) [12]. These bacteria are most common in patients who have had previous courses of antibiotics, especially when they were inappropriate. For this, the use of antibiotics in the treatment of AECOPD must pursue three objectives: hasten the regression of the symptoms of acute exacerbation, avoid the deterioration of respiratory function and delay as much as possible the occurrence of the next episode of exacerbation.

For years, an antibiotic treatment strategy has been drawn up; it consists of selecting the patients, classifying them into groups and then proposing an antibiotic or a list of antibiotics for each group. This selection is based on the Anthonisen classification combined with another classification proposed by the Canadian Thoracic Society. The latter distinguishes COPDs in three classes according to their severity: uncomplicated, complicated and at-risk class for Pseudomonas infections [20]. Macrolides or new cephalosporins were the antibiotics of choice for uncomplicated AECOPD. For the complicated class AECOPDs, the antibiotics of choice are amoxicillin-clavulanic acid and the new fluoroquinolones with Levofloxacin as the lead. An important point has been reported since the recommendations of the AFSSPS, SPILF and

Antibiotics Strains	AMX	AMC	GM	CS	OFX	CIP	LVX	RA	SXT	Total
Acinetobacter spp	R	R	-	-	-	R	-	-	-	
Acinetobacter baumanni	R	R	R	S	R	R	-	-	R	
Acinetobacter baumanni	R	R	S	S	-	R	-	-	-	
Branhamella catarrhalis	R	S	S	-	-	S	-	S	-	
Escherichia coli	R	R	S	S	S	-	-	S	S	
Escherichia coli	-	-	-	-	-	-	-	-	-	
Escherichia coli	R	S	S	S	R	R	-	-	R	
Haemophilus influenzae	S	S	S	-	-	-	-	S	-	

Haemophilus influenzae	S	S	-	-	-	-	-	-	-	
Haemophilus influenzae	S	S	R	-	-	R	-	S	S	
Haemophilus parainfluenzae	-	S	-	-	-	S	-	-	-	
Pseudomonas aeruginosa	-	-	S	S	-	S	-	-	-	
Pseudomonas aeruginosa	-	-	S	S	-	S	-	-	-	
Pseudomonas aeruginosa	-	-	S	S	-	R	-	-	-	
Pseudomonas aeruginosa	-	-	R	-	-	S	-	-	-	
Pseudomonas aeruginosa	-	-	R	S	-	R	-	-	-	
Pseudomonas aeruginosa	-	-	R	-	-	R	-	-	-	
Pseudomonas aeruginosa	-	-	-	S	-	S	-	-	-	
Pseudomonas aeruginosa	-	-	S	S	-	R	-	-	-	
Staphylococcus aureus	-	-	-	-	S	S	S	S	-	
Streptococcus pneumoniae	-	-	R	-	-	S	S	S	R	
Streptococcus pneumoniae	S	-	R	-	-	IT	R	S	R	
Streptococcus pneumoniae	S	-	R	-	-	IT	S	-	-	
Klebsiella pneumoniae	R	IT	S	S	R	R	-	R	R	
Klebsiella pneumoniae	R	IT	R	S	S	S	-	R	S	
Acinetobacter spp / Providencia	R	R	S	S		R	-			
Klebsiella pneumoniae / Pseudomonas aeruginosa	R	R	R	S	S	S	-	R	S	
Klebsiella pneumoniae / Haemophilus influenzae	R	S	S	S	S	S	-	R		
Klebsiella pneumoniae / Proteus mirabilis	R	R	R	S	S	S	-	IT	S	
Nombre of strains of bacteria tested	17	16	23	16	9	25	4	12	10	132
Nombre of resistant strains of bacteria	12	7	11	0	3	11	1	4	5	54
% of resistant strains of bacteria	70.5	43.7	47.8	0	33.3	44	25	33.3	50	40.9

Table 3: Antimicrobial resistance of all strains isolated.

R: resistant; S: sensible; IT: Intermediate; AMX: Amoxicillin; AMC: Amoxicillin + AC. Clavulanic; GM: Gentamicin; CS: Colistin; OFX: Ofloxacine; CIP: Ciprofloxacin; LVX: Levofloxacin; RA: Rifamicin; SXT: Trimethoprime + Sulfamid; P: Penicillin G.

SPLF, the anti-pneumococcal fluoroquinolones (FQAP) should not be prescribed if the patient received a fluoroquinolone, whatever the indication, in the Last 3 months. It is recommended that they be used with caution in institutions (risk of transmission of resistant strains) and in elderly patients under systemic corticosteroid therapy (increased risk of tendinopathy). Ciprofloxacin, the only oral anti-pyocyanine drug, was the antibiotic of choice for a pyocyanic infection risk [21]. A treatment with amoxicillin-clavulanic acid or second-generation macrolides or the new quinolones appears to be the most appropriate and effective in the group of patients with the most severe AECOPD whose basic obstructive syndrome is severe requiring use of mechanical ventilation where the bacterial infection seems to play an important role. In these patients, the use of conventional antibiotics such as Amoxicillin is not recommended given the high level of bacterial resistance [22].

In a prospective randomized controlled, double-blind study [23], Nouira., *et al.* have shown the benefit of new fluoroquinolones in the treatment of AECOPD. Levofloxacin currently has the most stable activity against pneumococcus and *Haemophilus* with a resistance rate approaching 0% in the majority of countries where it was evaluated as is the case of the results of our study. But, it would be obvious that the decline was still insufficient to have a precise idea on this question. A high level of resistance to Amoxicillin-clavulanic acid has been observed in strains isolated in our study. While this association still remains effective on pneumococcus and *Haemophilus*.

Conclusion

It emerges from this epidemiological study on antimicrobial resistance that it was necessary to review the prescription of first-line antibiotics for these patients, especially for the abusive use of Amoxicillin-clavulanic acid. That can help in the management of these patients with AECOPD, enabling doctors to better manage the use of antibiotics required for routine testing of acquired resistance, and institute adequate isolation of infected patients to minimize the effect of infection and nosocomial transmission.

In prospective, to properly control the cases of repetitive exacerbations and the readmission to hospitals of patients for a re-exacerbation of COPD, and thus reduce the use of antibiotic therapy, studies can be made taking into account the genetic diversity between individual strains of a bacterial species, including changes in surface antigenic structures. Such variation in the surface antigenic structure of bacterial pathogens allows these organisms to escape the immunity of the preexisting host and cause recurrent infection.

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